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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,225	08/05/2003	Joseph Armand Picard	PC25300A	6509

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/634,225	PICARD ET AL.	
	Examiner	Art Unit	
	Deepak R Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,11 and 12* is/are rejected.

7)☒ Claim(s) *10 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13 are pending in this application.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-13, drawn to compounds of formula (I) wherein ring B is 1,2,4-thiadiazin-3-one (3rd formula in B definition), corresponding composition and method of use, classified in class 544, subclass 253+.

II. Claims 1-7 and 9-13, drawn to compounds of formula (I) wherein ring B is 1,3-diazin-3-one, corresponding composition and method of use, classified in class 544, subclass 10.

The inventions are distinct, each from the other because of the following reasons:

The compounds of Groups I-II are drawn to structurally dissimilar compounds. They are made independently and used independently. They would be expected to raise different issues of patentability if a compound of Group I was anticipated, the anticipatory reference would not necessarily render obvious a compound of group II or vice-versa. They are not art-recognized equivalents, they are separately classified and require separate burdensome searches both in the literature and computer databases.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and as shown by their classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Claude Purchase on March 4, 2004 a provisional election was made with traverse to prosecute the invention of Group II, claims 1-7 and 9-13. Affirmation of this election must be made by applicant in replying to this Office action.

Claim 8 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claim 10 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to the other claims in the alternative only. See MPEP § 608.01(n). Also, the claim refers to three other claims for different features (see B. 3.).

Claim 13 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to the other claims in the alternative only. Also, the claim refers to two other claims for different features, which is unacceptable according to MPEP § 608.01(n) B.3.

Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition for the treatment of arthritis, does not reasonably provide enablement for a composition useful for all the diseases recited in the instant claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claim is drawn to 'A pharmaceutical composition for the treatment of a condition.....' and recites a wide list of diverse disorders. MPEP § 2164.01(c) provides that "[W]hen a compound of composition claim is limited by a particular use, enablement of that claim should be evaluated based on that use". First, the methods recited in the instant claim include 'conditions' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The instant claim language covers diseases that are very difficult to treat, e.g., cancer, HIV infection, Alzheimer's, etc. and diseases that are yet to be discovered, for which there is no enablement provided. The list of conditions recited in the claims comprises of generic disease groups such as connective tissue, inflammatory, CNS..... skin disorders, and cancers. Substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or "not provided", see *Ex parte Jovanovics*, 211 USPQ 907, 909.

The activity for the claimed compounds disclosed in the specification is as metalloproteinase inhibitors, useful to treat the extensive list of diseases recited in instant claim. Biological assays are provided in the specification at pages 38-54 and it is concluded that the tested compound of formula (I) was effective in inhibition of cartilage damage and thus, useful in treating osteoarthritis, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. Animal model tests are provided to test for the activity of the compounds in the treatment of osteoarthritis only and there is no theory or explanation given providing nexus between this data and the assorted diseases recited in the instant claim. The disclosure is insufficient such that one of ordinary skill in the art would not be able to extrapolate the given data to activity of the compounds in all other conditions of the claims. Many of the claimed disorders, e.g., Alzheimer's disease, cancer, HIV infection, etc. have nothing in common with the provided animal models and have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the claimed compounds can treat the large list of diseases recited in the claim having diverse mechanisms.

Enablement for the scope of treating 'inflammatory diseases' generally is not present. For a compound or a genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any site or any part of the body. There is no common mechanism by which all, or even most inflammations arise. The claims also include 'inflammatory diseases', the mediators for which include bradykinin, serotonin, histamine, leukotriene, cytokine, and many others. Accordingly, treatments for

'inflammation or inflammatory diseases' are normally tailored to the particular type of inflammation, and there is no "magic bullet" against inflammation generally.

CNS diseases which includes "Neurodegenerative disorders" covers diverse disorders such as Alzheimer's disease, dementia, hereditary cerebellar ataxias, paraplegias, syringomyelia, phakomatoses, and much more, in fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). For example, Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease." (pg. 1994). Alzheimer's disease has no known cause and has been treated mostly by choline esterase inhibitors to prolong the activity of acetylcholine.

Further, the instant claim is also drawn to 'treatment of cancers in mammal, **including** human' - no compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of

cancers'. In reference to tumor growth and metastasis, Morris et al. (Invasion Metastasis, 1997) stated that "initial arrest and extravasation may be difficult to prevent" (see the PubMed Abstract enclosed). Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use in treating a diverse list of conditions.

2) The state of the prior art: There are no known single group of compounds of similar structure which have been demonstrated to treat the wide variety of conditions instantly recited.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Rasmussen et al., in a recent article (Pharmacol. Ther., Vol. 75, 1997) stated that "Randomized clinical trials, in particular in earlier-

stage disease, are required in order to fully characterize the therapeutic potential of this class of agents", see page 74, col. 1. Also, Chambers et al., in their review article (J. National Cancer Inst., Vol. 89, 1997) expressed that "Details of the mechanisms by which MMPs and their inhibitors contribute to creating an environment that favors the initiation and continued growth of primary and metastatic tumors remain to be elucidated, but are of key importance in cancer therapy". Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to protect a potential host from the disorders nor there are doses given for the treatment of the disorders commensurate in scope with the claims.

6) The breadth of the claims: The instant claims embrace the treatment of a multitude of generic conditions.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have

to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Applicant's attention is directed to MPEP § 2164.01(c) wherein it is stated "when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use." As the specification provides biological tests and assays for the enablement of the compounds as MMP inhibitors (see pages 38-48), appropriate amendment of the claim would overcome the rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9 and 11-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 1, page 68, line 21, a definition is provided for 'm' (see "M is an integer from 0-3"), however, the variable 'm' could not be located anywhere in the claim.

The remaining claims are included here because they are dependent claims and do not further resolve the above issue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claim1 is rejected under 35 U.S.C. 102(a) as being anticipated by Nagamatsu et al. (Heterocycles, April 2002). The instant claims read on the reference disclosed compounds, see compound no. 9k and 9l.

2. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Hayakawa et al., CAPLUS Abstract 133:4331 (2000). The instant claims read on reference disclosed compound, RN 271256-56-5.

3. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Zvezdina et al., CAPLUS Abstract 107:198225 (1987). The instant claims read on reference disclosed compound, RN 110950-94-2.

4. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Ivanov et al., CAPLUS Abstract 100:68258 (1984). The instant claims read on reference disclosed compound, RN 88696-65-5.

5. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kost et al., CAPLUS Abstract 90:72145 (1979). The instant claims read on reference disclosed compounds, RN 57491-47-1; 57491-49-3; 63803-95-2; 63803-96-3; 63803-97-4; and 63803-98-5.

6. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kranz et al., U.S. Patent No. 3,810,894. The instant claims read on reference disclosed compound, see the compound of Example 14.

Allowable Subject Matter

Claims 2-7 and 11-12 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The references of record do not teach or fairly suggest the claimed compounds.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Deepak Rao
Primary Examiner
Art Unit 1624

March 8, 2004